

### REMARKS

These amendments introduce no new matter into the disclosure of this application.

No fee is believed to be due with this amendment. However, if Applicants are in error, the Commissioner is authorized to charge required fees to Perkins Coie's Deposit Account No. **50-0665**.

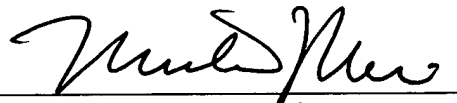
Respectfully submitted,

Perkins Coie LLP

Dated: \_\_\_\_\_

9/26/02

By: \_\_\_\_\_



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**VERSION WITH MARKINGS TO SHOW ALL CHANGES MADE**

Pursuant to 37 C.F.R. §§1.121(b)(iii) and 1.121(c)(3), the added matter to the specification and claims, i.e. “SEQ ID NO: \_\_,” is shown by underlining.

**IN THE SPECIFICATION**

On page 10, please delete paragraph [0028] and replace it with the following paragraph:

[0028] The invention includes a composition and method of treatment of animal pruritis. A preferred embodiment of the invention is composition for the treatment of animal pruritis comprising a therapeutically effective amount of one or more peptides having a COOH-terminal sequence consisting of KPV (SEQ ID NO:1), MEHFRWG (SEQ ID NO:2), HFRWGKPV (SEQ ID NO:3), and SYSMEHFRWGKPV (SEQ ID NO:4) in combination with a shampoo.

On page 11, please delete paragraph [0033] and replace it with the following paragraph:

[0033] The peptides in each of these preferred combination compositions has the primary sequence of KPV (SEQ ID NO:1) or VPK-Ac-CC-Ac-KPV. In a preferred composition, pharmacologically effective concentrations of the peptides may be as low as  $10^{-12}$  M but may be as high  $10^{-4}$  M.

On page 16, please delete paragraph [0062] and replace it with the following paragraph:

[0062] Figure 25 illustrates the anti-inflammatory effects of the KPV (SEQ ID NO:1) peptide, KPV (SEQ ID NO:1) dimer and prednisolone on edema induced in the hind paw of mice by the injection  $\alpha$ -carageenan as a function of time.

On page 16, please delete paragraph [0063] and replace it with the following paragraph:

[0063] Figure 26 illustrates a representation of the chemical structure of one form of the KPV (SEQ ID NO:1) dimer for use with one aspect of the invention.

On page 16, please delete paragraph [0067] and replace it with the following paragraph:

[0067]  $\alpha$ -MSH is a 13 amino acid with the primary sequence SYSMEHFRWGKPV (SEQ ID NO:4). In addition to anti-inflammatory properties, antibiotic and its anti-fungal properties, it also has anti-pyretic properties. The C-terminal tripeptide, KPV (SEQ ID NO:1), appears responsible for these properties. Lipton, J.M., *Antipyretic and Anti-inflammatory Lys-Pro-Val- Compositions and Methods of Use*, U.S. Patent No. 5,028,592, issued July 2, 1991; Lipton, J.M., *Antipyretic and Anti-inflammatory Lys-Pro-Val- Compositions and Methods of Use*, U.S. Patent No. 5,157,023, issued October 20, 1992; Catania, A., Lipton J.M.,  *$\alpha$ -Melanocyte Stimulating Hormone in the Modulation of Host Reactions*, 14 Endocr. Rev., 564-576 (1993); Lipton, J. M., Catania, A., *Anti-inflammatory Influence of the Neuroimmunomodulator  $\alpha$ -MSH*, 18 Immunol. Today, 140-145 (1997).

On page 18, please delete paragraph [0071] and replace it with the following paragraph:

[0071]  $\alpha$ -MSH (1-13) derivatives are also effective in the treatment of animal pruritis. Derivatives include biologically functional equivalents and hydropathic amino acids, as described in Example I, *infra*, as well as selected amino acid sequences within the native  $\alpha$ -MSH (1-13) chemical structure, i.e. KPV (SEQ ID NO:1), MEHFRWG (SEQ ID NO:2), HFRWGKPV (SEQ ID NO:3).

On page 18, please delete paragraph [0072] and replace it with the following paragraph:

[0072] One aspect of the invention is a composition and method of treatment of animal pruritis having an inflammatory bacterial and/or fungal component. A preferred embodiment of the invention is a composition for the treatment of animal pruritis comprising a therapeutically effective amount of one or more peptides having a C-terminal sequence consisting of KPV (SEQ ID NO:1), MEHFRWG (SEQ ID NO:2), HFRWGKPV (SEQ ID NO:3), and SYSMEHFRWGKPV (SEQ ID NO:4) in combination with a shampoo.

On page 19, please delete paragraph [0073] and replace it with the following paragraph:

[0073] Another preferred embodiment of the invention is a composition for the treatment of animal pruritis comprising a therapeutically effective amount of one or more peptides having a C-terminal sequence consisting of KPV (SEQ ID NO:1), MEHFRWG (SEQ ID NO:2), HFRWGKPV (SEQ ID NO:3), and SYSMEHFRWGKPV (SEQ ID NO:4) in combination with a therapeutically effective amount of a cortisol based glucocorticoid such as betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisone, prednisone, and triamcinolone and a shampoo.

On page 19, please delete paragraph [0077] and replace it with the following paragraph:

[0077] More preferably still, the peptides in each of these preferred combination compositions has the primary sequence of KPV (SEQ ID NO:1) or VPK-Ac-CC-Ac-KPV (Ac=Acetyl group). In all the preferred compositions, pharmacologically effective concentrations of the peptides may be as low as  $10^{-12}$  M but may be as high  $10^{-4}$  M.

On page 19, please delete paragraph [0078] and replace it with the following paragraph:

[0078] In yet another embodiment of the invention, one or one or more peptides having a C-terminal sequence KPV (SEQ ID NO:1),, such as KPV (SEQ ID NO:1), MEHFRWG (SEQ ID NO:2), HFRWGKPV (SEQ ID NO:3), and SYSMEHFRWGKPV (SEQ ID NO:4), which may or may not be in combination with therapeutically effective amounts of antibiotics, corticosteroids, and/or antifungals is dissolved in a carrier. Formulations for solution or solid based drug delivery carriers are well known in the art. Such preferred carriers include, but are not limited to, saline, phosphate buffered saline, gelatin, maltodextrin, cellulose, microcrystalline cellulose, methyl cellulose and carboxymethyl cellulose.

On page 21, please delete paragraph [0082] and replace it with the following paragraph:

[0082] By far, the most common cleansing agent used in the treatment of animals is a shampoo. Set forth below are examples of various formulations of the invention in different classifications of shampoos. Examples of some systemic preparations are also included showing the invention in those formulations. As used below the term “Active Ingredient” refers to one or more peptides having a C-terminal sequence of KPV (SEQ ID NO:1),, such as KPV (SEQ ID NO:1), MEHFRWG (SEQ ID NO:2), HFRWGKPV (SEQ ID NO:3), and SYSMEHFRWGKPV (SEQ ID NO:4). Preferably, the active ingredient is KPV (SEQ ID NO:1) or VPK-Ac-CC-Ac-KPV.

On page 25, please delete paragraph [0090] and replace it with the following paragraph:

[0090] Another preferred embodiment of the invention is a method for treating animal pruritis comprising systememic or topical application of a therapeutically effective level of  $\alpha$ -MSH, one or more peptides with a C-terminal sequence of KPV (SEQ ID NO:1) such as KPV (SEQ ID NO:1), and HFRWGKPV (SEQ ID NO:3). The peptides of this preferred method may be combined with a shampoo or therapeutically effective amounts of anti-inflammatories such as corticosteroids, fungicides, antibiotics, moisturizers or anti-itching compounds.

On page 28, please delete paragraph [0096] and replace it with the following paragraph:

[0096] Furthermore, these modified analogs of  $\alpha$ -MSH and/or its derivatives can also form dimers as exemplified by the KPV (SEQ ID NO:1) dimer in Figure 1.

On page 29, please delete paragraph [0099] and replace it with the following paragraph:

[0099] As mentioned above, excoriation may create open lesions as well as those typically associated with the underlying pathology. These open lesions may be secondarily infected by opportunistic skin pathogens; *Staphylococcus Aureus*, *Pityrosporon sp.* or *Tricophyton rubrum*, for example. It is well known that steroid therapy has a tendency to “mask infection” by suppressing the host response to infection. Although the suppression of the inflammatory response is desirable for the reduction of pain, edema and erythema, the inflammatory response is integral to the host defense mechanism against infection. Steroids used alone may ameliorate the pruritis and the symptoms associated with inflammation but may allow an infection to go unnoticed and to become serious and, in systemic infection, be life threatening.  $\alpha$  MSH (11-13), KPV

(SEQ ID NO:1), has been shown to have both antibacterial and antifungal properties and therefore does not present the same risk of masking an infection.

On page 31, please delete paragraph [0105] and replace it with the following paragraph:

[0105] These results show that  $\alpha$ -MSH (1-13), its C-terminal tripeptide  $\alpha$ -MSH (11-13), and other  $\alpha$ -MSH fragments have significant fungicidal effects against *C. albicans*. The most effective of the  $\alpha$ -MSH peptides were those including the C-terminal amino acid sequence KPV (SEQ ID NO:1) of the  $\alpha$ -MHS sequence, i.e.,  $\alpha$ -MSH (1-13),  $\alpha$ -MSH (6-13) and  $\alpha$ -MSH (11-13). In addition, the sequence VPK-Ac-CC-Ac-KPV has also been shown to be at least as effective as  $\alpha$ -MSH (11-13) against microbes. The  $\alpha$ -MSH core sequence (4-10), which is known to influence learning and memory, but has little antipyretic and anti-inflammatory influence, was effective, but less so. The ACTH peptides (1-39) and (18-39) did not have significant candidacidal effects. These observations indicate that antifungal activity is not common to all melanocortin peptides, but rather is specific to  $\alpha$ -MSH amino acid sequences, and most particularly to the C-terminal amino-acid sequences of  $\alpha$ -MSH. This strongly suggests that  $\alpha$ -MSH (1-13), its C-terminal tripeptide  $\alpha$ -MSH (11-13), and other  $\alpha$ -MSH fragments could serve as a basis for a therapeutic treatment for pruritis having a fungal component.

On page 35, please delete paragraph [0116] and replace it with the following paragraph:

[0116] Example VII suggests that systemic or topically administered  $\alpha$ -MSH may be useful in reducing the inflammation associated with animal pruritis. Example VII further suggests that such applications of  $\alpha$ -MSH would be clinically therapeutic for the

treatment of animal sinusitis, commonly associated with allergic pruritis. The anti-inflammatory activity of the tripeptide  $\alpha$ -MSH (11-13), KPV (SEQ ID NO:1), was demonstrated through the use of an animal model developed by Sparrow and Wilhelm (1957), J. Physiol., 137:51-65. This model relies on the principal that localized, subcutaneous injections of histamine will result in a localized increase in capillary permeability. When the test animal has been pretreated with blue dye intravenously, the localized histamine injections will elicit blue-colored wheals around the injection site. Thus, by pre-administration of an effective anti-inflammatory agent the blue color of the histamine-induced wheals will be much less pronounced, with the amount of color reduction being dependent on the relative amount and/or potency of the anti-inflammatory agent used.

On page 39, please delete paragraph [0121] and replace it with the following paragraph:

[0121] The results of this experiment are shown in Fig. 7. As will be appreciated from this data, except for the first hour when hydrocortisone markedly inhibited swelling ( $p < 0.05$ , Mann-Whitney test), there was no significant difference in the inhibition of paw edema caused by the tripeptide and hydrocortisone ( $p < 0.20$ ). These results indicated that the tripeptide inhibits inflammation as well as the classic anti-inflammatory agent, when given in an equal dose by weight, albeit with a slightly different time course. Based on the present results and the known effects of hydrocortisone and inflammation, it may be concluded that the tripeptide Lys-Pro-Val (SEQ ID NO:1) can be used to reduce inflammation associated with pruritis.



IN THE CLAIMS

WHAT IS CLAIMED IS:

1. (Amended) A veterinary composition for the treatment of animal pruritis comprising:
  - a) a therapeutically effective amount of at least one polypeptide with a terminal sequence KPV (SEQ ID NO:1); and
  - b) a shampoo
2. (Amended) The veterinary composition of claim 1 wherein the at least one polypeptide with a terminal sequence KPV (SEQ ID NO:1) is selected from a group consisting of KPV, VPK-Ac-CC- Ac-KPV, HFRWGKPV (SEQ ID NO:3), SYSMEHFRWGKPV (SEQ ID NO:4), or a biologically functional equivalent of any of the foregoing.
4. (Amended) A method of treating animal pruritis comprising:
  - a) administration of a therapeutically effective amount of at least one polypeptide with a terminal sequence KPV (SEQ ID NO:1); and
  - b) administration via a shampoo
5. (Amended) The method of claim 4 wherein the at least one polypeptide with a terminal sequence KPV is selected from a group consisting of KPV (SEQ ID NO:1), VPK-Ac-CC-Ac-KPV, HFRWGKPV (SEQ ID NO:3), SYSMEHFRWGKPV (SEQ ID NO:4), or a biologically functional equivalent of any of the foregoing.
7. (Amended) A veterinary composition for the treatment of animal pruritis comprising:
  - a) a therapeutically effective amount of at least one polypeptide with a terminal sequence KPV (SEQ ID NO:1);

b) a shampoo; and

c) a therapeutically effective amount of an anti-inflammatory agent.

8. (Amended) The veterinary composition of claim 7 wherein the at least one polypeptide is selected from the group consisting of KPV (SEQ ID NO:1), VPK-Ac-CC-Ac-KPV, HFRWGKPV (SEQ ID NO:3), SYSMEHFRWGKPV (SEQ ID NO:4), or a biologically functional equivalent of any of the foregoing.

14. (Amended) A method of treatment of animal pruritis comprising:

a) an administration of a therapeutically effective amount of at least one polypeptide with a terminal sequence KPV (SEQ ID NO:1);

b) an administration of a therapeutically effective amount of an anti-inflammatory agent;

and

c) an administration of a shampoo.

15. The method of treatment in claim 14 wherein the at least one polypeptide with an terminal sequence KPV is selected from a group consisting KPV (SEQ ID NO:1), VPK-Ac-CC-Ac-KPV, HFRWGKPV (SEQ ID NO:3), SYSMEHFRWGKPV (SEQ ID NO:4), or a biologically functional equivalent of any of the foregoing.

21. (Amended) A veterinary composition for the treatment of animal pruritis comprising:

a) a therapeutically effective amount of at least one polypeptide with a terminal sequence KPV (SEQ ID NO:1);

b) a shampoo; and

c) a therapeutically effective amount of an antibiotic.

22. (Amended) The veterinary composition of claim 22 wherein the at least one polypeptide is selected from the group consisting of KPV (SEQ ID NO:1), VPK-Ac-CC-Ac-KPV, HFRWGKPV (SEQ ID NO:3), SYSMEHFRWGKPV (SEQ ID NO:4), or a biologically functional equivalent of any of the foregoing.

25. (Amended) A method of treatment of pruritis in animals consisting of:

a) administration of a therapeutically effective amount of at least one polypeptide with a terminal sequence KPV (SEQ ID NO:1);

b) administration a shampoo; and

c) administration of a therapeutically effective amount of an antibiotic.

26. (Amended) The method of treatment of claim 26 wherein the at least one polypeptide is selected from the group consisting of KPV (SEQ ID NO:1), VPK-Ac-CC-Ac-KPV, HFRWGKPV (SEQ ID NO:3), SYSMEHFRWGKPV (SEQ ID NO:4), or a biologically functional equivalent of any of the foregoing.

29. (Amended) A veterinary composition for the treatment of animal pruritis comprising:

a) a therapeutically effective amount of at least one polypeptide with a terminal sequence KPV (SEQ ID NO:1);

b) a shampoo; and

c) a therapeutically effective amount of an antifungal.

30. (Amended) The veterinary composition of claim 30 wherein the at least one polypeptide is selected from the group consisting of KPV (SEQ ID NO:1), VPK-Ac-CC-Ac-KPV, HFRWGKPV (SEQ ID NO:3), SYSMEHFRWGKPV (SEQ ID NO:4), or a biologically functional equivalent of any of the foregoing.

33. (Amended) A method of treatment of pruritis in animals consisting of:
- a) administration of a therapeutically effective amount of at least one polypeptide with a terminal sequence KPV (SEQ ID NO:1);
  - b) administration a shampoo; and
  - c) administration of a therapeutically effective amount of an antifungal.
34. (Amended) The method of treatment of claim 34 wherein the at least one polypeptide is selected from the group consisting of KPV (SEQ ID NO:1), VPK-Ac-CC-Ac-KPV, HFRWGKPV (SEQ ID NO:3), SYSMEHFRWGKPV (SEQ ID NO:4), or a biologically functional equivalent of any of the foregoing.

IN THE ABSTRACT

Please delete the paragraph in the Abstract and replace it with the following paragraph.

The present invention is directed to a treatment for animal pruritis. One aspect of this invention involves a treatment for animal pruritis comprising one or more polypeptides with an amino acid sequence KPV (SEQ ID NO:1), VPK-AC-CC-AC-KPV, HFRWGKPV (SEQ ID NO:3), SYSMEHFRWGKPV (SEQ ID NO:4) for animal pruritis caused by exposure to any number of agents or causes. The polypeptides are at a level to effectively treat the animal pruritis and are combined with a shampoo. Other combinations include the polypeptides at a level to effectively treat animal pruritis combined with a shampoo and an antibiotic, antifungal and/or and anti-inflammatory. The one or more polypeptides can also be a dimer formed from any of the amino acid sequence above.